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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/017,743	02/03/98	SETTE	A 018623-00805

HM12/0831
TOWNSEND AND TOWNSEND AND CREW
TWO EMBARCADERO CENTER 8TH FL
SAN FRANCISCO CA 94111-3834

EXAMINER	
DIBRINO,M	
ART UNIT	**PAPER NUMBER**
1644	20

DATE MAILED: 08/31/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/017,743	Sette et al
Examiner	**Group Art Unit**
Marianne DiBrino	1644

☒ Responsive to communication(s) filed on Mar 28, 2000, 10/7/99, 1/18/00, 8/30/99, 6/13/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 8-70 is/are pending in the applicat

Of the above, claim(s) 11, 13, 18, 19, 31, 33, 37, 38, 50, 51, 56, and 57 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 8-10, 12, 14-17, 20-30, 32, 34-36, 39-49, 52-55, and 58-70 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4, filed 2/1/1999

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicants' responses filed 3/28/00, 10/7/99, 1/18/00 and the amendments filed 8/30/99 and 6/13/00 are acknowledged and have been entered.

Claims 8-70 are pending.

2. Applicants' election with traverse in Paper No. 18, filed 6/13/00 , of the peptide FPIPSSWAF, which is SEQ ID NO: 2, and an "other molecule" that is a CTL epitope, with traverse, is acknowledged. The traversal is for the reasons of record in Paper No. 18, namely that the group election requirement should be withdrawn on the basis that the claims of group II modify the breadth of the embodiment of the claims of group I, that there is no undue burden to examine all the claims, that the species election disregards key aspects of the invention, is confusing and there is no undue burden to examine all the species together.

3. In view of Examiner's meeting with BPS Richard Schwartz on 7/26/00 and Applicant's traversal, the Examiner has modified the election in the instant application to require the election of one ultimately disclosed species of peptide, i.e., a specific SEQ ID NO, and one ultimately disclosed species of "other molecule", and to eliminate the requirement for the Groups and the species of "motif" as well as for the species enunciated in items # 6, 7, 8 and 9 of the Restriction Requirement mailed 5/8/00 (Paper No. 16). Therefore, Applicants' election, as detailed in item #2 of this Action supra, fulfills the Restriction Requirement made by the Examiner.

Claims 8-10, 12, 14-17, 20-30, 32, 34-36, 39-49, 52-55 and 58-70 read on the elected species, SEQ ID NO: 22 and CTL epitope, and are currently being examined.

Claims 11, 13, 18, 19, 31, 33, 37, 38, 50, 51, 56 and 57 (non-elected species) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 18.

4. The instant application claims priority to 08/590,298 in the first line of the specification (and the declaration). The first line of the specification also lists "related" applications. If Applicant intends to claim priority to said related applications, then the word "related" needs to be deleted. As currently stated, and in view of the declaration, the instant application only claims priority to 08/590,298.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 8-10, 12, 14-17, 20-30, 32, 34-36, 39-49, 52-55 and 58-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection is a new matter rejection.

The added material which is not supported by the original disclosure is as follows:

(1) an "epitope consisting of about 8-11 residues that will bind to multiple HLA alleles". The instant specification discloses on page 3 at lines 10-13 "The oligopeptides of the invention...usually consist of between about 8 and about 11 residues". Applicants point to page 2, lines 22-37 for support for an "epitope consisting of about 8-11 residues", however, the specification discloses that "immunogenic peptides are about 9-10 residues in length. Applicants also point to page 3, line 24 to page 4, line 2 for support, however, said disclosure is "The term "motif" refers to the pattern of residues in a peptide of defined length, usually about 8 to about 11 amino acids, which is recognized by a particular MHC allele." There is no disclosure of an "epitope consisting of about 8-11 residues".

(2) "a structural supermotif". The instant specification discloses on page 3 at lines 26-27 the term "supermotif", but the instant specification does not disclose the term "structural supermotif".

(3) "proviso that the immunogenic peptide does not comprises an entire native antigen". Applicants point to support in the specification on page 4 at lines 9-10. However, lines 9-10 on page 4 disclose "Isolated peptides of this invention do not contain such endogenous co-purified protein [components which normally accompany material as found in its native state, lines 3-5]."

(5) "a non-naturally occurring" peptide. Applicants point to support in the instant specification on page 13 at lines 31-32, however, the specification disclose "peptides...of the invention can also be modified by altering the order or composition of certain residues...".

(6) "a non-naturally occurring" peptide. Applicants point to support in the instant specification on page 24 at lines 9-20, however, the specification disclose "A preferred means of administering nucleic acids encoding the peptides of the invention uses minigenes...".

(7) "an antigen derived from a pathogenic agent". The instant specification discloses on page 18 at lines 6-11, peptides from viral antigens and cancer antigens.

(8) a peptide or supermotif-comprising fragment thereof which comprises an IC50 of less than about, 50nM for at least one HLA molecule. Applicants point to the specification on page

57, Table 14 for support. Although some of the peptides listed in Table 14 have "an IC50 of less than, 50nM there is no disclosure in the instant specification of an IC50 of less than about 50nM.

(9) a peptide that is immunogenic "in vitro or in vivo". Applicants point to the specification on page 7, lines 22-28, however, page 7 is Table 1, a table disclosing exemplary amino acid residue substitutions.

(10) "wherein the immunogenic peptide...is more than about 11 amino acid residues in length."

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 8-10, 12, 14-17, 20-30, 32, 34-36, 39-49, 52-55 and 58-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how to make and/or use an isolated nucleic acid and pharmaceutical composition, thereof, comprising a non-naturally occurring nucleic acid encoding an immunogenic peptide, said immunogenic peptide comprising an epitope consisting of about 8-11 amino acid residues comprising a structural supermotif, or a nucleic acid encoding a heteropolymer comprising said immunogenic peptide. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass methods of inducing an immune response where no immune response will occur.

For purposes of examination, the instant claims are given their broadest reasonable interpretation. Therefore, said peptide can consist of up to one amino acid residue less than an entire native antigen. In addition, heteropeptides of undefined length and composition are encompassed by the instant claims. Such additional amino acid residues could prevent complex formation between said peptides and the HLA molecules. For instance, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding

site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends." (Engelhard at page 14, column 1, lines 23-27.) The minimum amount of peptide required to span the binding groove and make favorable contacts with their N-and C-termini may be dependent upon the sequence of the peptide itself since different amino acid residues have different physicochemical properties, and may be dependent upon the identity of the additional amino acids, since these residues may make a negative contribution to binding. Accordingly, there is a high level of unpredictability in designing/selecting longer sequences that would still maintain binding function, and applicant does not provide direction or guidance to do so.

In addition, the peptide that comprises a "structural supermotif", binds to an HLA molecule and induces a CTL response, however, there is no guarantee that said peptide would bind to HLA and induce a CTL response, i.e., there is no guarantee that said peptide that binds to HLA would be immunogenic. The specification is not enabling for the claimed method "whereby a CTL response is induced". The specification provides no evidence that the motif-bearing peptides of the claimed method are immunogenic. Celis et al (Molec. Immunol. Vol. 31(18), pages 1423-1430, 1994) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA and inducing a CTL response. Celis et al teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens." Ochoa-Garay et al (Molec. Immunol. Vol. 34, pages 273-281, 1997) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses (especially page 279, last sentence and continuing onto page 280). Karin et al (J. Exp. Med., Vol. 180, pages 2227-2237) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is

immunogenic. The claimed invention recites a motif wherein residues not involved in MHC binding are not specified. Karin et al teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1). Thus Karin et al establish that amino acid residues not recited in the claimed peptide (e.e., amino acid residues not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptides recited in the claims are immunogenic. Although the instant claims 77-79, 107-109, 115, 124-125, 133, 142 and 143 recite an IC_{50} value for a peptide binding to an HLA molecule, it would require undue experimentation to determine which of the trillions of peptides encompassed by the claimed invention are immunogenic and which are not.

Further, synthetic peptides that are chosen on the basis of "scanning" the protein of interest for potential peptide sequences that have a motif for binding to an HLA molecule or molecules may not necessarily contain a T cell epitope, and therefore, may not induce a CTL response. In addition, the specification does not disclose if the elected species of peptide SEQ ID NO: 22, FPIPSSWAF, actually is immunogenic.

There is insufficient guidance in the specification as to how to practice the method of the instant invention. There is no disclosure in the specification as to what additional amino acid residues outside the epitope are permissive for binding of the peptide to HLA molecules and which binding peptides would contain a T cell epitope and be immunogenic. Undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 8-10, 12, 14-17, 20-30, 32, 34-36, 39-49, 52-55 and 58-65 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 8, 15, 16, 28, 35, 53 and 54 are indefinite in the recitation of "non-naturally occurring" because it is not clear what is meant.

b. Claims 26 and 64 are indefinite in the recitation of "selected from the peptides of Tables 5, 6, or 7" because it is not clear. It is suggested that Applicants amend said claims to recite the SEQ ID NO of the peptides appearing in Tables 5, 6 and 7.

11. The invention is drawn to an isolated nucleic acid encoding an immunogenic peptide comprising an epitope which comprises a structural supermotif associated with peptide binding to multiple HLA molcules, and pharmaceutical composition thereof. With regard to application of prior art, the filing date of the instant claims is that of the instant application, i.e., 2/3/98, because the scope of the claimed invention is not disclosed in parent application 08/590,298. The parent application does not support the claimed method; in minimis, the parent application does not disclose a nucleic acid encoding an immunogenic peptide comprising an epitope *consisting of about 8-11 residues* which comprises a *structural* supermotif associated with peptide binding to multiple HLA molcules, and said parent application *does not disclose the elected species* FPIPSSWAF.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 8-10, 12, 14-17, 20-26, 28-30, 32, 34-36, 39-45, 47-49, 52-55, 58-64 and 70 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sidney et al (J. Immunol. Vol. 157, 1996, pages 3480-3490) in view of WO 93/03764.

For the purpose of examination, claims are given their broadest reasonable interpretation. "non-naturally occurring" is interpreted by the Examiner to encompass peptides that are synthesized.

Sidney et al teach an 'anchor fixed' nonamer peptide with the sequence FPIPSSWAF that was altered at position 1 in the base peptide IPIPSSWAF (HBV env 313), said base peptide being derived from the hepatitis B virus envelope protein (especially Table VI and Discussion section on pages 4388-3489). Sidney et al teach that the peptide FPIPSSWAF binds an HLA molecule at IC50 values ranging from 105 nM to 1.2 nM and binds with higher affinity than the base peptide IPIPSSWAF (especially Table VI). Said peptide has Pro at position 2 and Phe at position 9 and is associated with binding to multiple HLA molecules.

Sidney et al do not teach an isolated nucleic acid encoding a peptide comprising FPIPSSWAF.

WO 93/03764 teaches peptides from hepatitis B virus (HBV) that stimulate CTL are useful in the treatment and prevention of HBV infection, that said peptides can be formulated as HBV vaccines and pharmaceutical compositions and that said peptides are also useful in diagnostic methods (especially Abstract and page 23, lines 25-31). WO 93/03764 further teaches that peptides of the invention can be synthesized chemically or by recombinant DNA technology wherein a nucleotide sequence which encodes said peptide, or a heteropolymer comprising said peptide in fusion with another peptide that is a CTL epitope or a Th epitope, is inserted into an expression vector, transformed or transfected into an appropriate host cell and cultivated under conditions suitable for expression (especially page 22, lines 6-33, page 23, lines 3-24 and page 31, lines 13-23). WO 93/03764 teaches a DNA construct encoding a peptide (especially claim 59) which is used for the expression of said peptide.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an isolated nucleic acid molecule encoding the peptide FPIPSSWAF of Sidney et al because Sidney et al teach said HBV-derived peptide is immunogenic and WO 93/03764 teaches nucleic acids encoding immunogenic HBV-derived peptides.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce the peptide FPIPSSWAF of Sidney et al, or larger peptides comprising said peptide, for treatment of HBV as taught by WO 93/03764.

14. Claims 27, 46 and 65-69 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sidney et al (J. Immunol. Vol. 157, 1996, pages 3480-3490) in view of WO 93/03764 as applied to claims 8-10, 12, 14-17, 20-30, 32, 34-36, 39-49, 52-55, 58-65 and 70, and further in view of U.S. Patent No. 5,580,859.

For the purpose of examination, claims are given their broadest reasonable interpretation. "non-naturally occurring" is interpreted by the Examiner to encompass peptides that are synthesized.

Sidney et al and WO 93/03764 have both been discussed supra. The combined references do not teach a pharmaceutical composition comprising a nucleic acid molecule that encodes a peptide comprising FPIPSSWAF. The combined references do not teach a nucleic acid that comprises a viral vector.

U.S. Patent No. 5,580,859 discloses a pharmaceutical product comprising a polynucleotide, operatively coding for a biologically active immunogenic peptide (including viral promoters and vectors, especially column 11, lines 8-17 and Example 16), in solution in a physiologically acceptable injectable carrier and suitable for introduction interstitially into a tissue to cause

cells of the tissue to express the polypeptide encoded for by the said polynucleotide (especially column 5, lines 21-38, column 7, lines 60-67, column 8, lines 1-9 and 43-55). U.S. Patent No. 5,580,859 further discloses that administration of said pharmaceutical product to a human may serve to vaccinate said human or an animal, or it may serve a therapeutic purpose (especially column 5, lines 21-38).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a pharmaceutical composition comprising an isolated nucleic encoding the peptide FPIPSSWAF of Sidney et al because Sidney et al teach said HBV-derived peptide is immunogenic and WO 93/03764 teaches nucleic acids encoding immunogenic HBV-derived peptides.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to administer a nucleic acid encoding the peptide FPIPSSWAF of Sidney et al or larger peptides comprising said peptide, for treatment of HBV as taught by WO 93/03764.

15. No claim is allowed.

16. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Marianne DiBrino, Ph.D.
Patent Examiner/Group 1640/Technology Center 1600
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RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800 1600